Lipoprotein(a) and risk of sudden cardiac death in middle-aged Finnish men: A new prospective cohort study

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Acknowledgement of grant support: The Academy of Finland, Helsinki, Finland; City of Kuopio, Kuopio, Finland; Finnish Medical Foundation, Helsinki, Finland, and Finnish Cultural Foundation, Helsinki, Finland, supported the Kuopio Ischemic Heart Disease Study. These sources had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Conflicts of interest: The authors report no relationships that could be construed as a conflict of interest.

Keywords: Lipoprotein(a); risk factor; risk prediction; sudden cardiac death

Abbreviations

BMI = body mass index

CHD = coronary heart disease

CRP = C-reactive protein

CVD = cardiovascular disease

FPG = fasting plasma glucose

HDL-C = high-density lipoprotein cholesterol

HR = hazard ratio

KIHD = Kuopio Ischaemic Heart Disease

Lp(a) = lipoprotein(a)

LVH = left ventricular hypertrophy

SCD = sudden cardiac death

SD = standard deviation

SBP = systolic blood pressure

ABSTRACT

Background: Lipoprotein(a) [Lp(a)] is an established and independent risk factor for cardiovascular outcomes. However, the relationship of Lp(a) with risk of sudden cardiac death (SCD) is unknown. We aimed to assess the association of Lp(a) with risk of SCD in the Kuopio Ischemic Heart Disease prospective cohort study of 1,881 men aged 42-61 years at recruitment.

Methods and Results: Plasma Lp(a) concentration was assessed at baseline and repeat measurements made several years apart. After a median follow-up of 24.7 years, 141 SCDs were recorded. Hazard ratios (HRs) (95% confidence intervals [CI]) were assessed and were corrected for within-person variability in Lp(a) levels. The regression dilution ratio of $\log_e$ Lp(a) adjusted for age was 0.84 (95% CI: 0.81-0.88). Lipoprotein(a) levels were log-linearly associated with risk of SCD. In analyses adjusted for established risk factors, the HR (95% CI) for SCD per 1 standard deviation (3.56-fold) higher baseline $\log_e$ Lp(a) was 1.24 (1.05-1.47; $P = 0.013$). This remained consistent on further adjustment for alcohol consumption, resting heart rate, lipids, and C-reactive protein 1.23 (1.04-1.46; $P = 0.018$). HRs remained unchanged after accounting for incident coronary events and did not vary importantly in several relevant clinical subgroups. Adding Lp(a) to a SCD risk prediction model did not significantly improve risk discrimination beyond established risk factors, but improved the continuous net reclassification 30.2% (1.1 to 59.2%, P=0.042).

Conclusions: Available evidence shows a continuous and independent association between Lp(a) levels and risk of SCD. Further research is needed to replicate these findings.

1. Introduction

Lipoprotein (a) [Lp(a)], a liver derived lipoprotein composed of a central core with apolipoprotein B100 (apo B_{100}) covalently bound to apolipoprotein (a) [apo(a)],[1] is an established and independent risk factor for myocardial infarction (MI), coronary heart disease (CHD),stroke, heart failure, and calcific aortic stenosis.[2-5] There are also suggestions of causal relationships between Lp(a) and these outcomes.[3-5]

Though Lp(a) pathophysiology is still not fully understood, there is evidence to suggest that that Lp(a) contributes to the development of CHD via pro-atherogenic and pro-inflammatory activities.[6] Sudden cardiac death (SCD) is a global public health problem accounting for 15-20% of all deaths[7] with CHD being the most common pathology underlying SCD.[8] Despite reported declines in CHD incidence over the past decades due to major advances in its treatment and prevention,[9, 10] SCD rates have declined to a lesser extent;[11] suggesting that CHD may not be the underlying cause for a fraction of SCDs. Given that CHD and SCD have shared risk factors[12] and the established relationship between Lp(a) and CHD, we hypothesized that serum Lp(a) would be linked to the risk of SCD. In addition, though established atherosclerotic risk factors explain a large proportion of the risk of SCD,[13] its pathogenesis is still not fully established as it appears other additional factors may be involved. These established risk factors are often absent in a large proportion of SCD victims,[14] which makes the identification of individuals at increased risk a difficult undertaking. Lipoprotein(a) may represent a substantial residual risk in mediating SCD and could be a novel causal risk factor or a risk predictor for SCD. However, to date, there has been no previous prospective evaluation of the association of Lp(a) with SCD.

To clarify this issue, our first objective was to evaluate in detail, the nature and magnitude of the prospective association of Lp(a) with risk of SCD in a population-based cohort of 1,881 apparently healthy men from eastern Finland. The second objective was to assess the consistency of the association in important clinical subgroups. Finally, we investigated the extent to which plasma Lp(a) measurements

could improve the prediction of SCD when added to conventional risk factors. In subsidiary analyses, we also assessed the associations of Lp(a) with out-of-hospital SCDs and non-SCDs.

2. Materials and methods

This study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology.[15]

2.1. Study population

Participants in the current study consisted of a representative sample of men living in the city of Kuopio and its surrounding rural communities in eastern Finland who were recruited into the Kuopio Ischemic Heart Disease (KIHD) risk factor study. This population-based prospective study was designed to investigate risk factors for CVD and other chronic diseases. Study participants were 42-61 years of age during baseline examinations performed between March 1984 and December 1989. Of 3433 potentially eligible and randomly selected men, 3235 were found to be eligible for the study. Of this number, 2682 (82.9 %) volunteered to participate, 186 did not respond to the invitation and 367 declined to give informed consent. For the present analysis, men with a prevalent history of heart failure (HF) and cardiac arrhythmias were excluded. The current analysis included 1,881 men with non-missing information on plasma Lp(a), relevant covariates, and outcomes. The research protocol and study was approved by Research Ethics Committee of the University of Eastern Finland and each participant gave written informed consent.

2.2. Ascertainment of outcomes

We included all SCDs that occurred from study enrollment through to 2012. No losses to follow-up were recorded in the KIHD study. Participants (using Finnish personal identification codes) are under continuous annual surveillance for the development of new CVD events, including incident cases and

deaths.[16] The sources of information on SCD and other outcomes were based on a comprehensive review of all available hospital records, wards of health centres, informant interviews, health practitioner questionnaires, study electrocardiograms (ECGs), death certificate registers, and medico-legal reports. The diagnostic classification of SCDs was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80% of all cardiac deaths), and history of CHD together with the clinical history and findings from hospital and paramedic staff. A death was determined to be an SCD when it occurred within 1 hour of the onset of an abrupt change in symptoms or within 24 hours after the onset of symptoms; including nonwitnessed cases when clinical and autopsy findings did not reveal a non-cardiac cause of sudden death or after successful resuscitation from ventricular tachycardia and/or ventricular fibrillation.[17] The witnessed subject was to have been seen alive and symptom free within one hour before the event. Sudden cardiac deaths that occurred in out-of-hospital conditions were also defined as events that occurred in places that had been reported accurately in hospital documents.[17] Documents were cross-checked in detail by two physicians. Cardiac deaths that did not lead to death during the following 24 hours of the onset of symptoms were considered as non-SCDs. The Independent Events Committee, masked to clinical data, performed classification of outcomes.

2.3. Measurement of risk factors

The collection of blood samples, physical measurements, lifestyle characteristics, and measurement of serum lipids, lipoproteins and glucose have been described in detail in previous reports.[18, 19] The cholesterol content of lipoprotein fractions were measured from fresh samples after combined ultracentrifugation and precipitation, and serum triglycerides were assessed enzymatically (Boehringer Mannheim, Mannheim, Germany).[20] Measurement of Lp(a) concentrations were made from frozen plasma samples stored at -20° C for 2-6 years, using a radioimmunoassay (Mercodia Apo(a) RIA, Mercodia AB, Uppsala, Sweden). Repeat measurements of Lp(a) were performed 4 years and 11 years after the baseline measurements, during the follow-up period in a random subset of participants. Fasting

plasma glucose (FPG) was measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany) after protein precipitation by trichloroacetic acid. C-reactive protein (CRP) was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). Standard resting 12-lead ECG was also recorded and heart rate was defined. The ECG criterion for left ventricular hypertrophy (LVH) was based on either the Sokolow-Lyon or Romhilt-Estes point score as described previously.[18, 19]

2.4. Statistical analysis

We log-transformed values of skewed variables to achieve normal distributions. Descriptive analyses were performed to summarize the baseline characteristics of the participants. The standard deviation (SD) of baseline loge Lp(a) concentration was 1.27, corresponding to approximately four-fold higher circulating Lp(a) (ie, $e^{1.27}$=3.56). The partial correlation coefficients were calculated using linear regression models adjusted for age, to assess the cross-sectional associations of Lp(a) with various risk markers. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. The assumptions of the proportionality of hazards were confirmed using Schoenfeld residuals.[21] To assess the shape of the association between Lp(a) and SCD risk, HRs were calculated within quartiles of baseline Lp(a) and plotted against mean Lp(a) levels within each quartile. Floating variances were used to calculate 95% confidence intervals for the log hazard ratio in each group (including the reference group), to allow for comparisons across the groups irrespective of the arbitrarily chosen reference category (bottom quartile)[26]. As the association showed a continuous shape, HRs were calculated per 3.56-fold (ie, 1-SD) higher Lp(a) levels. In subsidiary analysis, HRs were also calculated by quartiles defined according to the baseline distribution of plasma Lp(a) levels. Hazard ratios were adjusted for age, BMI, systolic blood pressure (SBP) prevalent CHD, smoking status, history of diabetes mellitus, LVH, history of hypertension, use of medications (antihypertensive agents and lipid-lowering drugs), alcohol consumption, resting heart rate, triglycerides, high-density lipoprotein cholesterol (HDL-

C), and CRP. We performed subgroup analyses using interaction tests to assess statistical evidence of any differences in hazards across levels/categories of pre-specified individual level characteristics, including age at survey, smoking status, history of diabetes mellitus, history of hypertension, LVH, BMI, SBP, and CRP. To minimize biases as a result of including possible cases with prevalent but undetected CHD, heart failure, and cardiac arrhythmias, sensitivity analysis involved excluding the first five years of follow-up. Given that most exposures in epidemiological studies are subject to fluctuations within individuals over time and are measured with error, analysis using only baseline measurements of the exposure could underestimate the true strength of any aetiological association between exposure and disease outcome (i.e. "regression dilution bias"[22]). We therefore quantified and corrected for within-person variability in levels of Lp(a), that is, the extent to which an individual's Lp(a) measurements vary around a long-term average level exposure ("usual levels");[23] which was achieved by estimating adjusted regression dilution ratios (RDRs), calculated by regressing available repeat measurements on baseline values.[24] Finally, to assess whether adding information on plasma Lp(a) measurements to established SCD risk factors is associated with improvement in prediction of SCD risk, we calculated measures of discrimination for censored time-to-event data (Harrell's C-index [25]) and reclassification (the continuous net-reclassification-improvement [NRI], a category-free version of the NRI).[26] Measures of discrimination and reclassification were assessed for the risk model (age, SBP, cigarette smoking, serum low density lipoprotein cholesterol, history of diabetes, BMI, previous myocardial infarction, family history of CHD, and cardiorespiratory fitness) as previously described.[17, 27]All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

3. Results

3.1. Baseline characteristics and correlates of lipoprotein(a)

The mean age at entry was 53 (SD, 5) years. The median (interquartile range) of Lp(a) at baseline was 9.66 (3.84-22.04) mg/dl (**Table 1**). Plasma Lp(a) levels were weakly and inversely correlated with

physical measures (BMI and blood pressure), triglycerides, and fasting plasma glucose. Weak positive correlations were observed for total cholesterol (r = 0.12) and CRP (r = 0.10). Baseline Lp(a) levels were significantly lower in men with diabetes compared with men without diabetes (**Table 2**). During a median (IQR) follow-up of 24.7 (19.6-26.3) years (41,071 person-years at risk), there were 141 SCDs (annual rate 3.43/1000 person-years at risk, 95% confidence interval (CI) 2.91 to 4.05). Of the total SCDs, 109 occurred out-of-hospital. There were 68 non-SCDs.

3.2. Correction for within-person variability

Serial measurements of Lp(a) taken 4 years and 11 years after baseline over 24.7 years, were available in a random sample of 633 men, providing a total of 1,176 repeat measurements of Lp(a). Overall, the regression RDR of loge Lp(a), adjusted for age, was 0.84 (95% CI: 0.81to 0.88), suggesting that the associations using one-off or baseline measurements of Lp(a) with SCD would only under-estimate the association by [1/0.84)-1]*100=19%.

3.3. Lipoprotein(a) and risk of sudden cardiac death

Cumulative hazard curves demonstrated a greater risk of SCDs among males in the top quartile of Lp(a) levels compared to those in the bottom quartile (*P* = 0.032 for log-rank test; **Figure 1**). In analysis adjusted for conventional risk factors (age, BMI, SBP, prevalent CHD, smoking status, history of diabetes mellitus, LVH, history of hypertension, use of antihypertensive agents and lipid-lowering drugs), there was a continuous association of Lp(a) with risk of SCD, which was potentially consistent with either a curvilinear or log-linear shape. However, statistical tests suggested a better fit with a log-linear shape (*P* for linearity = 0.006) (**Figure 2**). The HR per 1 SD change in baseline $\log_e$ Lp(a) concentration was 1.24 (95% CI: 1.05 to 1.47; *P* =0.013) in analysis adjusted for established risk factors, which remained consistent on further adjustment for alcohol consumption, resting heart rate, triglycerides, and HDL-C 1.23 (95% CI: 1.04 to 1.46; *P* = 0.018) and further for CRP 1.20 (95% CI: 1.01 to 1.43; *P* = 0.039). The

HR remained materially unchanged after further adjusting for incident coronary events (**Table 3)**. The positive associations were maintained in analyses by quartiles of the baseline distribution of Lp(a) levels (**Table 3**). The findings were qualitatively similar on correction for regression dilution (**Appendix Supplement 1**). Hazard ratios did not vary importantly by age, BMI, SBP, HDL-C, triglycerides, CRP, history of diabetes mellitus, smoking status, history of hypertension, and prevalent CHD (**Figure 3**), and the main results remained the same in analyses that excluded the first five years of follow-up (data not shown). A SCD risk prediction model containing established risk factors yielded a C-index of 0.7526 (95% CI: 0.7154 to 0.7898). After addition of information on plasma Lp(a) to the model, the C-index was 0.7531 (0.7162 to 7901), yielding a non-significant increase of 0.0005 (-0.0030 to 0.0041; *P*=0.776). The continuous NRI was 30.2% (1.1 to 59.2%, *P*=0.042).

In separate analyses for out-of-hospital SCDs and non-SCDs, there was no significant evidence of any association of Lp(a) with these outcomes (**Appendix Supplement 2**).

4. Discussion

In this population of middle-aged men without a history of HF and cardiac arrhythmias at baseline, we observed an increase in risk of SCD with increasing levels of Lp(a), though further work is required to determine whether a curvilinear or log-linear shape would better describe the relationship. The association remained consistent after adjustment for several established risk factors, other potential confounders, and on accounting for incident coronary events during follow-up. The overall findings did not vary importantly across several subgroups. Our reproducibility studies of Lp(a) indicate that Lp(a) concentration is consistent within individuals over several years. Addition of information on plasma Lp(a) measurements to several established risk factors for SCD, did not incrementally improve SCD risk prediction, but yielded a significant improvement in reclassification. Finally, no significant associations were observed for the outcomes of out-of-hospital SCDs and non-SCDs.

4.1. Comparison with previous work

It is not possible to compare the current findings in the context of previous work, as a we were unable to locate any published reports that have evaluated the prospective association between Lp(a) levels and SCD events. However, several epidemiological and genetic studies have consistently and robustly shown that elevated Lp(a) is independently associated with CVD.[2-4] This association has been demonstrated for CVD specific endpoints such as acute myocardial infarction,[4] CHD,[28] carotid atherosclerosis,[29] ischemic stroke,[30] aortic valve stenosis,[31] and heart failure.[5] There is accruing evidence suggesting that these associations are also causal.[4, 31] Our novel findings of a robust independent association between elevated Lp(a) and risk of SCD is therefore not surprising, given that SCD and these CVD outcomes share many common risk factors. Indeed, coronary artery disease is the most common underlying cause of SCD in the general population.[8] However, given that this is the first prospective study to evaluate this association, other large-scale prospective studies are still needed to confirm the current findings.

4.2. Possible explanations for findings

Consistent with results observed for studies that have evaluated other cardiovascular outcomes, [2, 5] the pathophysiological mechanisms of action underlying our findings of a continuous and independent association between Lp(a) and SCD may relate to the pro-atherogenic, prothrombotic, and pro-inflammatory properties of Lp(a).[6] Elevated Lp(a) is highly atherogenic through its low-density lipoprotein (LDL) component.[6] Indeed, experimental data has demonstrated the presence of Lp(a) in human atherosclerotic plaques,[32] which also provides evidence that Lp(a) is involved in the development of atherosclerotic lesions.[6] Thus, via its involvement in atheromatous plaque formation,[33, 34] Lp(a) may also cause acute myocardial ischemia, which is the most common trigger for fatal arrhythmias.[35] Lipoprotein(a) may inhibit fibrinolysis and promote thrombosis through competitive inhibition of plasmin generation and inactivation of the tissue factor pathway inhibitor.[36,

37] Lipoprotein(a) is able to mediate pro-inflammatory effects via its carriage of oxidized phospholipids, which are also known to be pro-atherogenic.[38] The atherosclerotic lesions and vulnerable plaques found in majority of cases of SCD have been found to be characterised by pathological signs of inflammation.[39] Lipoprotein(a) has also been implicated in macrophage foam cell formation, smooth muscle cell proliferation, plaque inflammation, and instability, which are key stages in the development of vulnerable atherosclerotic lesions.[36, 37] Liporotein(a) may also promote SCD via an increased risk of CHD; however, our analysis involved adjustment for prevalent CHD and our results remained robust on accounting for incident nonfatal CHD events during follow-up. We also excluded the first five years of follow-up thus minimizing the possibility of SCDs due to undiagnosed CHD. Further research is needed to help unravel the mechanistic pathways of Lp(a) in the pathogenesis of SCD.

The findings of a continuous and independent association between Lp(a) levels and SCD risk are consistent with the indication of a causal relationship, but this requires robust evidence from randomized controlled trials. However, such trials may not enable causal inferences, as pharmacological agents [such as niacin, cholesteryl ester transfer protein (CETP) inhibitors, PCSK9 inhibitors, and antisense oligonucleotides] that are able to modify levels of Lp(a),[40] also influence concentrations of other lipoproteins (HDL-C, LDL-cholesterol, triglycerides, apo B100, and oxidised phospholipids).[41, 42] In the absence of clinical trials however, Mendelian randomisation (MR) studies of genetic variants specifically related to Lp(a) levels may provide another route to assess causality.[43] Plasma levels of Lp(a) are primarily genetically determined by polymorphisms in the *LPA* gene which code for the apo(a) moiety of Lp(a). Genetic variants including the kringle IV repeats at this locus, which have pronounced effects on Lp(a) concentrations,[44] have been used to assess the causal role of Lp(a) in CVD outcomes using MR approaches.[3-5]

4.3. Implications of findings

Our findings are novel and highlight a clear and independent link between elevated Lp(a) levels and the risk of SCD in the general population and suggest that Lp(a) might modify the risk of SCD. Though there has been considerable debate and interest in the therapeutic modulation of Lp(a) levels, there is currently lack of clinical evidence that lowering of Lp(a) levels would decrease cardiovascular risk. Reasons for this include: (i) it is estimated that up to about 90% of the variation in Lp(a) levels may be due to genetic factors, making it one of the most important genetic risk factor for CVD.[45] As Lp(a) levels are primarily determined by genetic factors, its circulating levels are not influenced by dietary or environmental effects. Evidently, interventions such as nutritional and lifestyle modification have not shown any benefits in decreasing levels of Lp(a); (ii) in addition, given that interventions that specifically lower Lp(a) levels are currently not available, it has been difficult to perform intervention trials to establish the clinical benefit of lowering levels of Lp(a); and (iii) even though novel pharmacological agents such as niacin, mipomersen, PCSK9, and CETP inhibitors, do significantly lower Lp(a) levels, the reductions do not translate into clinical benefit on CVD outcomes[46, 47] or may not actually be related to the effects of Lp(a) lowering.[48] Irrespective of these shortcomings and still not fully acknowledged as a CVD risk factor in clinical practice, plasma Lp(a) is still regarded as a promising though unproven strategy for the prevention of major cardiovascular outcomes such as SCD. Though there is no unanimous agreement by guideline bodies as to when to measure Lp(a) and how to treat elevated levels, advice by expert panels of guideline bodies such as the European Atherosclerosis Society, National Lipid Association, and the National Cholesterol Education Program Adult Treatment Panel, have stressed the need to screen for elevated Lp(a) levels in patients at moderate- to high-risk of CVD/CHD and modulating levels to desirable levels of < 50 mg/dl with the use of niacin.[49-51] In the absence of (i) specific guideline recommendations on when and how to treat Lp(a) levels; (ii) promising new drugs that are still being tested;[52] and (iii) trials in patients with isolated Lp(a) elevations which will show a clinical benefit on cardiovascular outcomes; a major hope for isolated lowering of Lp(a) levels with potential clinical benefit on cardiovascular outcomes has been demonstrated in recent lipoprotein

apheresis studies.[53, 54] Finally, though addition of plasma Lp(a) did not significantly improve SCD risk prediction beyond established risk factors in this population, it does not rule out the potential for Lp(a) assays to be used in the identification of individuals at high risk for SCD. We observed a net reclassification improvement and our risk prediction analyses were limited, as we did not have complete measurements on some other risk markers (e.g., ECG parameters, measures of heart rate variability, measures of ejection fraction, and angiographic findings) used in clinical risk prediction algorithms for SCD.[55, 56] The potential usefulness of Lp(a) in SCD risk prediction deserves further investigation.

4.4. Strengths and limitations

There are several notable strengths of the current study that deserve consideration. This is the first prospective evaluation of the association between circulating plasma Lp(a) levels and the risk of SCD. Our analyses were based on a large cohort that was selected to be a nationally representative population-based sample of middle-aged Finnish men. The cohort was well characterised, involved a high response rate, involved a long follow-up period, and there were no losses during follow-up, minimising the risk of selection bias. Participants in the KIHD cohort have been annually monitored using established databases for outcome events. We had access to a comprehensive panel of lifestyle and biological markers, which allowed adequate adjustment for potential confounding, enabling reliable assessments of the associations. Repeat measurements of Lp(a) several years apart enabled correction for long-term within-person variability in Lp(a) levels. Indeed, reproducibility substudies of Lp(a) in the KIHD were consistent with findings from Emerging Risk Factors Collaboration.[2] Our study had a number of limitations which also deserve consideration. We included a relatively small number of SCDs, therefore the need to confirm these findings in larger-scale studies with more SCD events. Though we adjusted for several confounders, there is always the possibility of residual confounding, which could in part explain the association between Lp(a) and SCD. The KIHD study included only middle-aged men based on a predominantly white-European population from eastern Finland and given that plasma levels of Lp(a) vary substantially

among persons and populations,[57] our findings therefore cannot be generalizable to women, the young, elderly, and other ethnicities.

Conclusions

This prospective study shows a continuous and independent association between Lp(a) levels and risk of SCD. However, further research is needed to replicate these findings and assess the potential clinical utility of Lp(a) as a risk assessment tool or validated causal therapeutic target for SCD events.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

We thank the staff of the Kuopio Research Institute of Exercise Medicine and the Research Institute of Public Health and University of Eastern Finland, Kuopio, Finland for the data collection in the study.

Sources of Funding

The Academy of Finland, Helsinki, Finland; Finnish Foundation for Cardiovascular Research, Helsinki, Finland, and Finnish Cultural Foundation, Helsinki, Finland, supported the Kuopio Ischemic Heart Disease Study. These sources had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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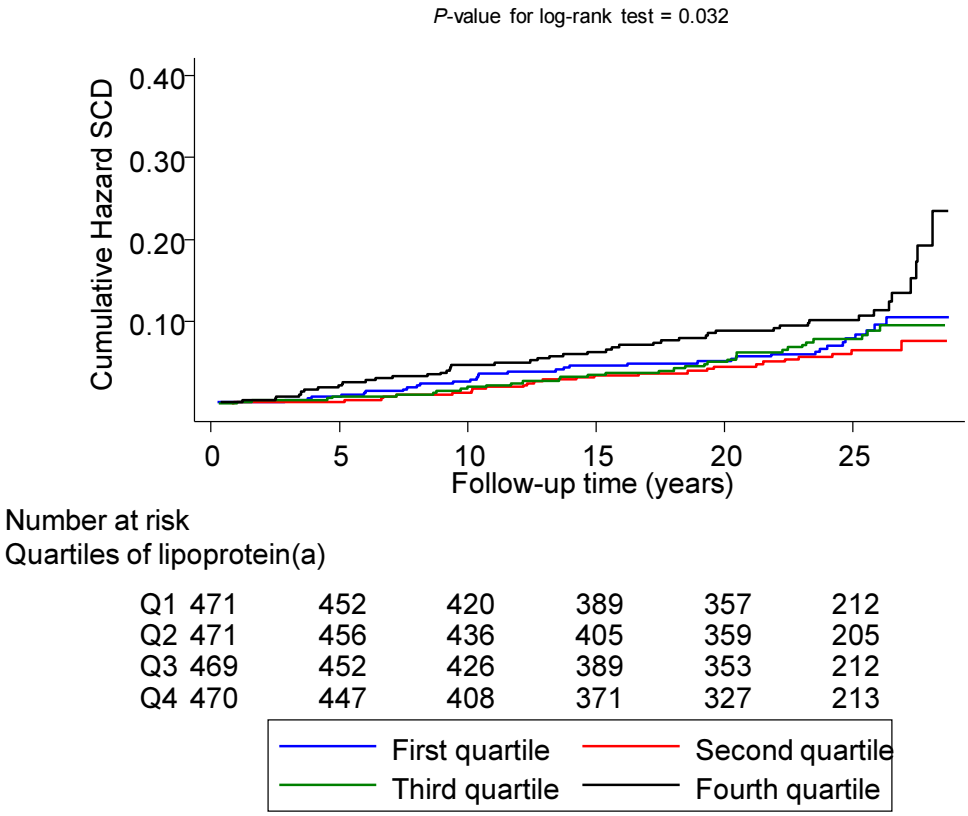
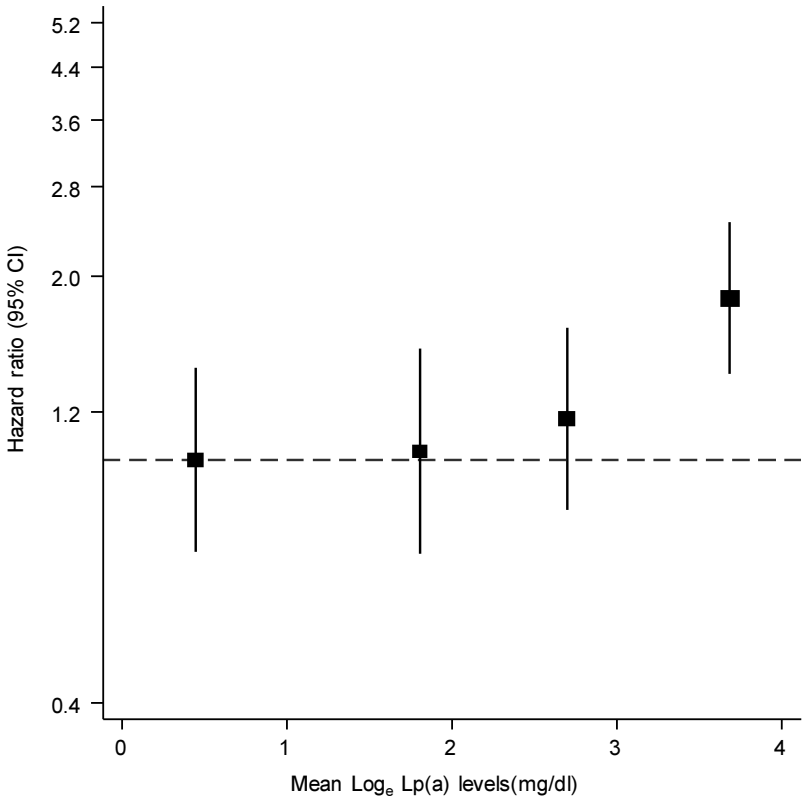
Figure 1: Cumulative hazard curves for sudden cardiac death by quartiles of lipoprotein(a)



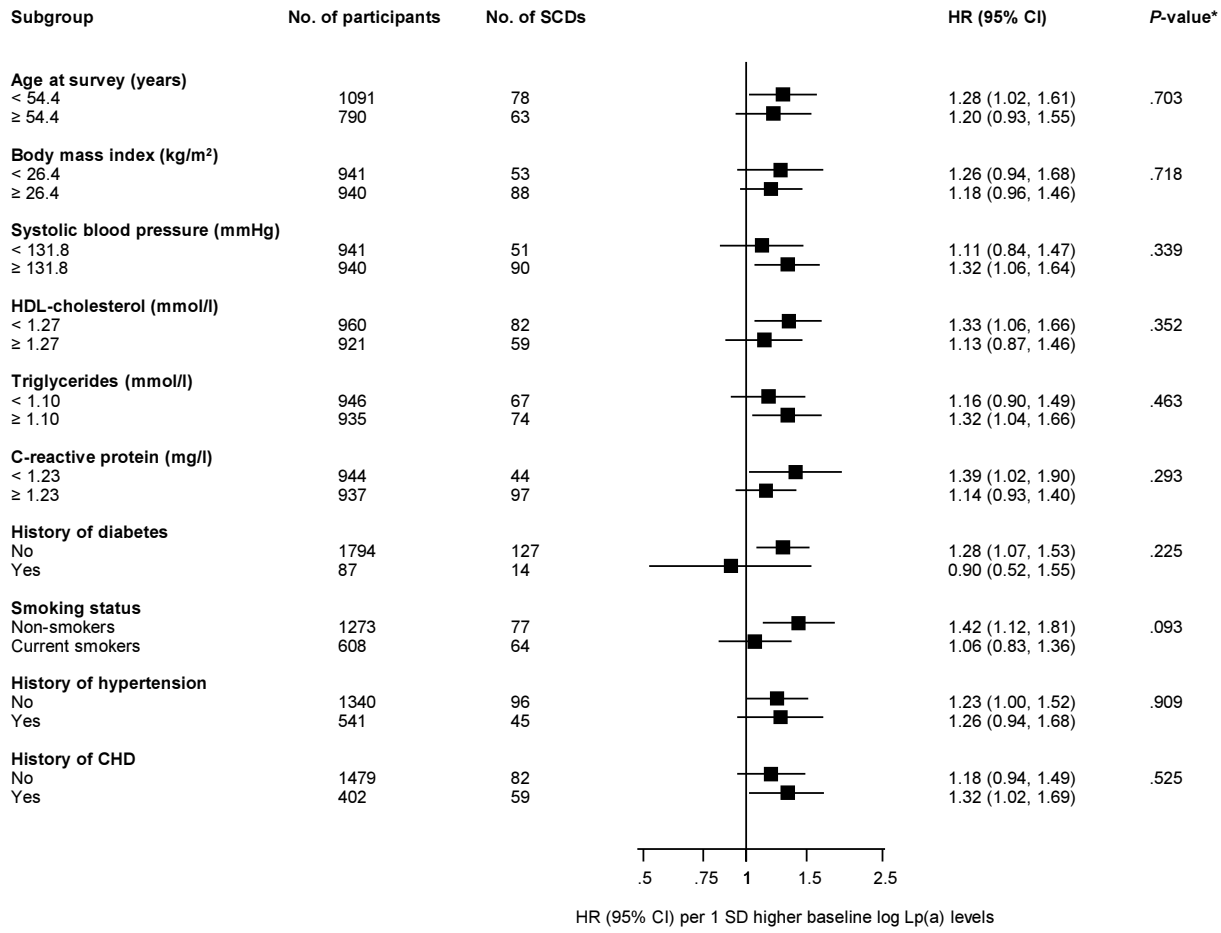
The median Lp(a) level (mg/dl) was 1.68 (range 0.84-2.92) for the lowest quartile; 6.16 (range 4.83-7.63) for the second quartile; 14.79 (range 12.13-18.26) for the third quartile; and 37.35 (range 28.46-51.72) for the top quartile; Lp(a), lipoprotein(a); SCD, sudden cardiac death

Figure 2: Hazard ratios for sudden cardiac death by quartiles of baseline levels of lipoprotein(a)



Hazard ratios were adjusted for age, body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs); Lp(a), lipoprotein(a)

Figure 3: Hazard ratios for baseline levels of lipoprotein(a) and sudden cardiac death risk by several participant level characteristics



Hazard ratios were adjusted for age, body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs); CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; Lp(a), lipoprotein(a); SCD, sudden cardiac death; SD, standard deviation; *, *P*-value for interaction

Table 1: Baseline participant characteristics

	Overall (N=1,881) Mean (SD) or n (%)	Without SCD (N=1,740) Mean (SD) or n (%)	With SCD (N=141) Mean (SD) or %	*P*-value
Log_e lipoprotein(a) (mg/dl)	2.16 (1.27)	2.15 (1.26)	2.31 (1.36)	0.107
Questionnaire/Prevalent conditions				
Age at survey (years)	53 (5)	52 (5)	54 (4)	0.001
Alcohol consumption (g/week)	76.0 (141.6)	74.3 (142.1)	97.3 (133.3)	0.063
History of diabetes	87 (4.6)	73 (4.2)	14 (9.9)	0.002
Current smokers	608 (32.3)	544 (31.3)	64 (45.4)	0.001
Left ventricular hypertrophy	21 (1.1)	19 (1.1)	2 (1.4)	0.723
History of hypertension	541 (28.8)	496 (28.5)	45 (31.9)	0.390
History of CHD	402 (21.4)	343 (19.7)	59 (41.8)	< 0.001
Use of anti-hypertensives	345 (18.3)	304 (17.5)	41 (29.1)	0.001
Medication for dyslipidemia	11 (0.6)	11 (0.6)	0 (0.0)	0.344
Physical measurements				
BMI (kg/m^2)	26.8 (3.5)	26.7 (3.4)	28.2 (4.2)	< 0.0001
SBP (mmHg)	134 (16)	134 (16)	139 (18)	0.0003
DBP (mmHg)	89 (10)	89 (10)	91 (10)	0.009
Resting heart rate (bpm)	62.5 (10.7)	62.3 (10.6)	64.5 (11.7)	0.025
Lipid markers				
Total cholesterol (mmol/l)	5.92 (1.09)	5.89 (1.08)	6.19 (1.13)	0.002
HDL-C (mmol/l)	1.29 (0.30)	1.29 (0.30)	1.23 (0.26)	0.018
Log_e triglycerides (mmol/l)	0.11 (0.50)	0.10 (0.50)	0.21 (0.56)	0.012
Metabolic and inflammatory markers				
Fasting plasma glucose (mmol/l)	5.32 (1.19)	5.29 (1.12)	5.69 (1.83)	0.0001
Serum creatinine (µmol/1)	89.4 (22.6)	89.3 (13.3)	91.0 (67.4)	0.409
Log_e CRP (mg/l)	0.29 (0.95)	0.26 (0.94)	0.66 (0.98)	< 0.0001

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure; SCD, sudden cardiac death

Table 2: Cross-sectional correlates of lipoprotein(a)

	Pearson correlation r (95% CI)†	Percentage difference (95% CI) in Lp(a) levels per 1 SD higher or compared to reference category of correlate‡
Log_e lipoprotein(a) (mg/dl)	-	-
Questionnaire/Prevalent conditions		
Age at survey (years)	0.02 (-0.03, 0.06)	2% (-4, 8)
Alcohol consumption (g/week)	0.00 (-0.04, 0.05)	0% (-5, 6)
History of diabetes		
No	-	Ref
Yes	-	-31% (-47, -9)*
Smoking status		
Other	-	Ref
Current	-	3% (-9, 16)
Left ventricular hypertrophy		
No	-	Ref
Yes	-	33% (-23, 129)
History of hypertension		
No	-	Ref
Yes	-	-9% (-20, 3)
History of CHD		
No	-	Ref
Yes	-	-3% (-16, 11)
Use of anti-hypertensives		
No	-	Ref
Yes	-	-14 (-26, 0)
Medication for dyslipidemia		
No	-	Ref
Yes	-	40% (-34, 197)
Physical measurements		
BMI (kg/m^2)	-0.10 (-0.15, -0.06)***	-12% (-17, -7)***
SBP (mmHg)	-0.02 (-0.07, 0.02)	-3% (-8, 3)
DBP (mmHg)	-0.04 (-0.08, 0.01)	-5% (-10, 1)
Resting heart rate (bpm)	0.01 (-0.03, 0.06)	1% (-4, 7)
Lipid markers		
Total cholesterol (mmol/l)	0.12 (0.08, 0.17)***	17% (11, 24)***
HDL-C (mmol/l)	0.00 (-0.05, 0.05)	0% (-6, 6)
Log_e triglycerides (mmol/l)	-0.05 (-0.10, -0.01)*	-6% (-11, -1)*
Metabolic and inflammatory markers		
Fasting plasma glucose (mmol/l)	-0.08 (-0.12, -0.03)**	-9% (-14, -4)**
Serum creatinine (µmol/1)	0.04 (-0.00, 0.09)	6% (-0, 12)
Log_e C-reactive protein (mg/l)	0.10 (0.06, 0.15)**	14% (8, 21)***

BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure; asterisks indicate the level of statistical significance: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$, †Pearson correlation coefficients between log_e Lp(a) and the row variables; ‡, Percentage change in Lp(a) levels per 1-SD increase in the row variable (or for categorical variables, the percentage difference in mean Lp(a) levels for the category versus the reference) adjusted for age

Table 3: Association of baseline plasma lipoprotein(a) concentrations with sudden cardiac death

Lp(a) concentration (mg/dl)	Events/ Total	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Per 1 SD increase	141 / 1881	1.24 (1.05 to 1.47)	0.013	1.23 (1.04 to 1.46)	0.018	1.20 (1.01 to 1.43)	0.039	1.21 (1.01 to 1.44)	0.039
Q1 (< 3.84)	34 / 471	ref		ref		ref		ref	
Q2 (3.85-9.66)	26 / 471	1.03 (0.61 to 1.74)	0.902	1.01 (0.60 to 1.70)	0.980	0.98 (0.58 to 1.65)	0.931	1.02 (0.60 to 1.72)	0.941
Q3 (9.67-22.04)	33 / 469	1.17 (0.72 to 1.90)	0.534	1.16 (0.71 to 1.88)	0.561	1.12 (0.69 to 1.83)	0.655	1.13 (0.69 to 1.85)	0.629
Q4 (≥ 22.05)	48 / 470	1.84 (1.17 to 2.88)	0.008	1.79 (1.14 to 2.82)	0.011	1.69 (1.07 to 2.67)	0.025	1.72 (1.09 to 2.73)	0.021

CI, confidence interval; HR, hazard ratio; Lp(a), lipoprotein(a); SD, standard deviation

Model 1: Adjusted for age, BMI, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes mellitus, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs)

Model 2: Model 1 plus alcohol consumption, resting heart rate, triglycerides, total cholesterol, and high-density lipoprotein cholesterol

Model 3: Model 2 plus C-reactive protein

Model 4: Model 3 plus incident coronary heart disease as a time-dependent covariate

Appendix 1: Association of Usual Levels of Plasma Lipoprotein(a) With Sudden Cardiac Death

Lp(a) concentration (mg/dl)	Events/ Total	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Per 1 SD increase	141 / 1881	1.29 (1.06 to 1.59)	0.013	1.28 (1.04 to 1.57)	0.018	1.24 (1.01 to 1.53)	0.039	1.24 (1.01 to 1.53)	0.039
Q1 (< 3.84)	34 / 471	ref		ref		ref		ref	
Q2 (3.85-9.66)	26 / 471	1.04 (0.56 to 1.93)	0.902	1.01 (0.54 to 1.88)	0.980	0.97 (0.52 to 1.81)	0.931	1.02 (0.55 to 1.91)	0.941
Q3 (9.67-22.04)	33 / 469	1.20 (0.67 to 2.15)	0.534	1.19 (0.66 to 2.12)	0.561	1.14 (0.64 to 2.05)	0.655	1.15 (0.64 to 2.07)	0.629
Q4 (≥ 22.05)	48 / 470	2.06 (1.21 to 3.53)	0.008	2.01 (1.17 to 3.44)	0.011	1.87 (1.08 to 3.22)	0.025	1.91 (1.10 to 3.30)	0.021

CI, confidence interval; HR, hazard ratio; Lp(a), lipoprotein(a); SD, standard deviation

Model 1: Adjusted for age, BMI, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes mellitus, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs)

Model 2: Model 1 plus alcohol consumption, resting heart rate, triglycerides, total cholesterol, and high-density lipoprotein cholesterol

Model 3: Model 2 plus C-reactive protein

Model 54 Model 3 plus incident coronary heart disease as a time-dependent covariate

Appendix 2: Associations of Baseline Lipoprotein(a) Concentrations With Out-of-Hospital Sudden Cardiac Deaths and Non-Sudden Cardiac Deaths

Models	**Out-of-hospital sudden cardiac death**		**Non-sudden cardiac death**	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
	1,881 participants and 109 cases		1,881 participants and 68 cases	
Model 1	1.17 (0.97 to 1.43)	0.097	1.02 (0.80 to 1.30)	0.897
Model 2	1.17 (0.96 to 1.42)	0.112	1.02 (0.80 to 1.30)	0.877
Model 3	1.16 (0.95 to 1.41)	0.140	1.00 (0.78 to 1.28)	0.998
Model 4	1.16 (0.95 to 1.41)	0.143	0.99 (0.77 to 1.27)	0.928

CI, confidence interval; HR, hazard ratio; Hazard ratios are per 1 standard deviation (3.56-fold) increase in lipoprotein(a) levels

Model 1: Adjusted for age, BMI, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes mellitus, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs)

Model 2: Model 1 plus alcohol consumption, resting heart rate, triglycerides, total cholesterol, and high-density lipoprotein cholesterol

Model 3: Model 2 plus C-reactive protein

Model 4: Model 3 plus incident coronary heart disease as a time-dependent covariate